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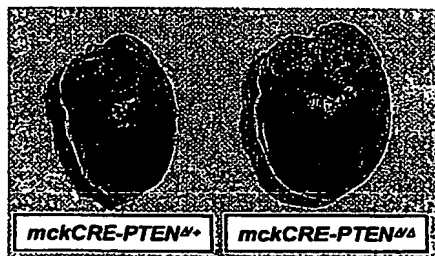
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(54) Title: COMPOSITIONS AND METHODS FOR TREATING HEART DISEASE



(57) Abstract: The PTEN/PI3K signaling pathway regulates a vast array of fundamental cellular responses. We show that cardiomyocyte-specific inactivation of tumor suppressor, PTEN results in hypertrophy, and unexpectedly, a dramatic decrease in cardiac contractility. Analysis of double mutant mice revealed that the cardiac hypertrophy and the contractility defects can be genetically uncoupled. PI3K γ mediates the alteration in cell size while PI3K γ acts as a negative regulator of cardiac contractility. Mechanistically, PI3K γ inhibits cAMP production and hypercontractility can be reverted by blocking cAMP function. These data show that PTEN has an important *in vivo* role in cardiomyocyte hypertrophy and GPCR signaling and identify a function for the PTEN-PI3K γ pathway in the modulation of heart muscle contractility.